Amendments to the Drawings

Figures 6A-7B and 10 have been amended to include the SEQ ID NOs.

Attachment: Replacement Sheet
Annotated Marked-Up Drawings

REMARKS

This Reply is set forth under appropriate subheadings for the convenience of the Examiner.

Amendments to the Specification

The specification has been amended to include the SEQ ID NO: of each sequence described in the specification.

No new matter has been added. Entry of the amendments to the specification is respectfully requested.

Amendment to Claims 4, 41, 43 and 44 and New Claims 47 and 48

Claims 4, 41, 43 and 44 have been amended to more clearly define that which Applicants regard as the invention. Support for the amendments to Claims 4 and 41 can be found in the specification and claims as originally filed. For example, page 44, lines 9-13 describes mutations that affect the RING finger domain and/or one of the NHL motifs of the protein, and original Claim 44 describes method for detecting the presence of, or predisposition to, Lafora's disease, thereby providing support for the amendments to Claims 4, 41, 43 and 44. Page 20, lines 11-13 describes insertion and deletion mutations, thereby providing support for the amendment to Claim 4. Page 2, lines 25-27 describes a method of detecting a mutation in the *EPM2B* gene (SEQ ID NO: 1) in a human, thereby providing support for the amendments to Claims 4, 41, 43 and 44. Page 11, line 24 through page 12, line 14 describes methods for detecting the EPM2B gene and page 22, lines 1-19 describes detecting specific mutations in the EPM2B gene, thereby providing support for new Claims 47 and 48.

No new matter has been added in the amendments to the claims or in new Claims 47 and 48. Entry of the amendments to Claims 4, 41, 43 and 44 and new Claims 47 and 48 is requested.

Restriction Requirement

In response to a Restriction Requirement, Applicants made an election of Group II and made a further species election with traverse on June 30, 2008. The Examiner maintained the restriction requirement and made it final. Non-elected subject matter has been withdrawn.

In accordance with M.P.E.P. § 821.04(a), Applicants respectfully request that if the method of detecting the presence of, or predisposition to Lafora's disease of Claim 4 is found to be allowable, then withdrawn Claims 6-25 directed to a method of detecting the presence of, or predisposition to Lafora's disease, comprising the detection of specific mutation should be rejoined and examined.

Rejection of Claims 4, 31, 41, 43 and 45 Under 35 U.S.C. § 112, First Paragraph

Claims 4, 31, 41, 43 and 45 were rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not disclosed in the specification in such as way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

Specifically, the Examiner states that "[t]he claims broadly encompass any mutation which is a missense, nonsense or frameshift mutation in SEQ ID NO: 1 which results in a 'deleterious effect' on the encoded protein product."

The Examiner further states that "no common structural attributes identify the members of the genus" and that "[t]he genus includes an enormous number of mutations for which no written description is provided in the specification."

Claim 31 has been canceled, thereby obviating the rejection as to this claim.

Claim 43, as amended, is directed to a method of detecting the presence or absence of a mutation in the nucleic acid sequence of the EPM2B gene (i.e., SEQ ID NO: 1) in a human; it is not directed to a mutation that results in a "deleterious effect" on the encoded protein product of SEQ ID NO: 1 as suggested by the Examiner. Thus, it is unclear why the Examiner has rejected Claim 43 under 35 U.S.C. § 112, first paragraph. In addition, Applicants have fully described the nucleic acid sequence of the EPM2B (SEQ ID NO: 1). Applicants have also provided ample description of the various methods for detecting a mutation in a nucleic acid sequence. For example, page 22, lines 1-19, describes a number of methods for detecting mutations. Thus,

Claim 43 meets the requirements of the written description requirement of 35 U.S.C. §112, first paragraph.

Claims 4, 41 and 45, as amended, are directed to a method of detecting Lafora's disease in a human comprising detecting a mutation in SEQ ID NO: 1 that affects a portion of the EPM2B gene encoding a RING finger domain or an NHL motif of SEQ ID NO. 1 and wherein the mutation is associated with the presence of, or predisposition to, Lafora's disease. Applicants' specification provides 21 examples of mutations that fall within the scope of the genus. (See Table 1). The specification discloses that these "[t]wenty-one distinct DNA sequence variations in EPM2B predicted to cause deleterious effects on the protein product, named malin, were found to co-segregate with [Lafora's Disease] in 39 families." (Specification at page 1, lines 25-27). Furthermore, the specification provides descriptions of each of these mutations that includes the differences between the mutated and wild-type protein, stating that "[a]ll of the mutation detected would affect the putative RING or NHL motifs, or would be predicted to lead to a frame-shift or cause drastic structural change in the protein." (Specification at page 44, lines 9-13). Thus, Applicants have described the common attributes of the genus, namely that the mutations affect a portion of the EPM2B gene encoding a RING finger domain or an NHL motif of SEQ ID NO:1.

The Examiner further states that

> [w]ith respect to the claims which encompass dog or canine mutations...[t]he specification analyzes a single breed of dogs, namely the miniature wirehaired dachshund (MWHD) ... The specification teaches all affected animals had bi-allelic expansions of [a] dodecamer repeat (page 51). This single expansion mutation is not with the scope of the claims, as it is not a missense, nonsense or [frameshift mutation].

Claims 4 and 41, as amended, are directed to a method of detecting Lafora's disease in a human. Additionally, Claims 4 and 41 have been amended to include insertion, deletion and point mutations to clarify that insertion/deletion mutations are encompassed within the scope of the claims.

Thus, Claims 4, 41, 43 and 45, as amended, satisfy the written description requirements of 35 U.S.C. §112, first paragraph.

Rejection of Claims 4-5, 26, 31, 41 and 43-46 Under 35 U.S.C. § 112, first paragraph

Claims 4-5, 26, 31, 41 and 43-46 were rejected under 35 U.S.C. § 112, first paragraph because the specification, while being enabling for a method of detecting Lafora's disease in a human subject comprising obtaining a sample from the human subject and detecting a G at position 205 of SEQ ID NO: 1 wherein the presence of a G at position 205 of SEQ ID NO: 1 is indicative of Lafora's disease, does not reasonably provide enablement for a method of detecting Lafora's disease in a mammal, including a human, by detecting a missense, nonsense or frameshift which results in a deleterious effect on the encoded protein product including a nucleotide change at position 205 of SEQ ID NO: 1. The Examiner stated that the specification does not enable any person skilled in the art to which it pertains, or with which it is nearly connected, to make and use the invention commensurate with the scope of the claims. The Examiner stated that Applicants' claims were evaluated for enablement based on the Wands factors as set forth in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988).

Claim 31 has been canceled, thereby obviating the rejection as to this claim.

The unpredictability of the art and the state of the prior art

The Examiner believes that the invention is in an unpredictable art field and supports the rejection with the citation of three references: Lucentini in The Scientist (2004), Hirschhorn *et al.* in Genetics in Medicine (2002), and Ioannidis in Nature Genetics (2001). The Examiner cites these three references to describe the inaccuracies present in the field of genetic testing. Lucentini discusses that most gene association studies are typically wrong and it is commonplace for follow-up studies to find that the original gene-disease association was inaccurate. Hirschhorn et al. discusses that genetic variations and associations are often irreproducible. Ioannidis also discusses the irreproducibility of early association studies. These references highlight the fact that early association studies can be misleading. The Examiner believes that there is insufficient guidance in the specification to overcome these art recognized problems to detect a mutation in the EPM2B gene and to then associate that mutation with Lafora's disease. Therefore, the Examiner believes that the methods are not enabled as broadly as written in the claims. Applicant respectfully disagrees.

Guidance in the specification

The Examiner states that the guidance in the specification amounts to an invitation to try to make and use the claimed invention, stating that the specification provides no evidence that all mutations in SEQ ID NO: 1 are associated with Lafora's disease.

However, the method of the claimed invention involves detecting a mutation that affects the RING finger domain or an NHL motifs of SEQ ID NO: 1. The evidence discovered by Applicants demonstrates that mutations in these specific regions of the protein encoded by SEQ ID NO: 1 are likely to be associated with Lafora's disease. Applicants teach specific mutations in these regions of the EPM2B gene that result in Lafora's disease. Applicants teach one of skill in the art where to look for additional mutations and provide the sequence of the wild-type EPM2B gene (that is, the EPM2B gene without mutations resulting in Lafora's disease) to serve as a control. Applicants provide a blue print for others to follow with specific directions which amount to more than just an "invitation to try" to use the claimed invention.

Quantity of Experimentation

The Examiner further states that while the skilled artisan could assay for additional mutations, it would have been unpredictable which mutations are indicative or diagnostic of Lafora's disease.

The Examiner has mischaracterized Applicants' claimed invention with respect to Claims 26, 43, 44 and 46. Claims 26, 44 and 46 are directed to detection of a specific mutation as listed in Table 1. Claim 43 is directed to a method of detecting the presence or absence of a mutation in the EPM2B gene (SEQ ID NO: 1) The method of detecting a known nucleic acid sequence, as well as the method for detecting a mutation in a known nucleic acid sequence, is well-known to one of ordinary skill in the art, even without the guidance provided in the specification. (See, for example, page 22, lines 1-19). Thus, Claims 26, 43, 44 and 46 meet the enablement requirements of 35 U.S.C. § 112, first paragraph.

Claims 4-5, 41 and 45, as amended, are directed to a method of detecting Lafora's disease in a human comprising detecting a mutation in SEQ ID NO: 1 that affects a portion of the EPM2B gene encoding a RING finger domain or an NHL motif of SEQ ID NO: 1. The specification provides ample description of the location of the RING finger domain and NHL motifs of the EPM2B gene and protein. (See, for example, page 14, lines 5-12 and Figure 6B).

This information, along with the description in the specification of the importance of the RING finger domain and NHL motifs enables one of skill in the art to practice the claimed methods. For example, the specification describes at least 17 mutations that are associated with Lafora's disease.

The claimed methods enable one of skill in the art to detect a mutation associated with the presence of, or predisposition to, Lafora's disease using no more than routine and standard techniques. Thus, claims 4-5, 41, 43 and 45, as amended, satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph and reconsideration and withdrawal of the rejection is respectfully requested.

Rejection of Claims 4-5, 26, 31, 41 and 45 Under 35 U.S.C. § 112, Second Paragraph

Claims 4-5, 26, 31, 41 and 45 were rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the Examiner stated that Claims 4-5, 26, 31 , 41 and 45 are indefinite because "It is unclear whether the claims are drawn to detecting Lafora's disease or merely detecting a mutation..."

Claim 31 has been canceled, thereby obviating the rejection as to this claim.

Claims 4-5, 26, 41 and 45 have been amended to clarify that the claimed method is directed to a method of detecting the presence of, or predisposition to, Lafora's disease.

In Claim 41 the Examiner believes that the term "substantial" in the claim is a relative term that is not defined by the claim and that the specification does not provide a standard for ascertaining the requisite degree. Claim 41 has been amended and no longer recites the term "substantial."

Thus, Claims 4-5, 26, 41 and 45 satisfy the requirements of 35 U.S.C. § 112, second paragraph, and reconsideration and withdrawal of the rejections is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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